PROLONGED EFFECTS OF LSD ON EEG RECORDS DURING DISCRIMINATIVE PERFORMANCE IN CAT; EVALUATION BY COMPUTER ANALYSIS.

24 p.

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UNPUBLISHED PRELIMINARY DATA

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INTRODUCTION

Psychotomimetic and hallucinogenic drugs exert their effects in man and animals for periods ranging from a few to many hours (Lear et al. 1959; Rothlin 1957). The biochemical basis of these effects has been sought in the case of lysergic acid diethyl amide (LSD) in complex metabolic interrelations between it and certain amines, particularly 5-hydroxytryptamine (serotonin), by Brodie and his colleagues (Brodie, Pletscher and Shore 1955; Shore, Silver and Brodie 1955). It has long been recognized, however, that other more subtle mechanisms might also be involved, since the usual behavioral symptoms and electrophysiological effects fail to appear when the doses are repeated at intervals shorter than a few weeks (Adey, Bell and Dennis 1962), and cross-habituation has been reported between hallucinogenic agents having no close structural interrelations (Balistrieri and Fontinari 1959; Jarvik and Chorover 1960).

Evaluation of EEG changes in the acute phase of drug action has implicated deep structures of the temporal lobe, and particularly the hippocampal system, for both psychotomimetic agents, such as cyclohexamine derivatives (Adey and Dunlop 1960), and for hallucinogenic agents, such as LSD and its derivatives, in both cat and monkey (Adey, Bell and Dennis 1962; Monroe and Heath 1961). Both types of drugs induced high amplitude, seizure-like wave discharges in hippocampal structures. In the cat, the abnormal wave trains induced by LSD appeared in brief bursts beginning and ending abruptly, particularly in conditions of reduced visual and auditory environmental stimuli. Their persistence in behavioral test situations was associated with a disruption of the learned performance. This defective behavior was associated with the propagation of the abnormal hippocampal activity into a variety of subcortical centers (Adey, Bell and Dennis 1962).

As a first approach to the detection of subtle but consistent changes in patterns of EEG activity over a period of many days following a single dose of LSD, we have here examined the wave trains accompanying performance of a learned discriminative task, from test data recorded on days before, during and following the drug. Our previous studies have examined the characteristics of these wave trains by a variety of computing techniques, including averaging, correlation, cross-spectral and phase modulation analyses (Adey, Dunlop and Hendrix 1960; Adey, Walter and Hendrix 1961; Adey and Walter 1963; Walter and Adey 1963). They have sought to establish the possibility of hidden patterns in the apparent imprecision of the EEG, on the premise that the slow, graded wave processes characteristic of cortical tissue might provide the basis for a signal system within cerebral structures, and perhaps relate to both transaction and storage of information characteristic of this tissue.

METHODS

Detailed data are presented here from two animals, which formed part of a series of 18 animals repeatedly exposed to LSD, psilocybin and psilocin (Adey, Bell and Dennis 1962). The limited number of animals analyzed in detail may be justified on grounds of the extended testing periods separating each dose of LSD. In this way, a very substantial baseline was secured, and each animal served in many respects as its own control.

Electrodes were chronically implanted in the dorsal hippocampi, the adjacent entorhinal (posterior pyriform) cortex, the amydaloid complex, the subthalamus, the rostral midbrain reticular formation. Screw electrodes were placed over the primary visual cortex. Behavioral training was

performed in a modified T-maze, with approach to food on the basis of a visual cue. Forty test runs were performed each day, and only those approaches were rewarded which were directly to the side of the T-maze displaying the visual cue. All drug tests were conducted after attainment of a stable performance level in excess of 90 per cent correct, and at a time when the animals might thus be regarded as over-trained. Solutions of LSD were prepared freshly for each experiment from crystalline material and administered by intraperitoneal injection. The doses were insufficient to impair performance capability, even when tested 1 to 2 hours after drug administration.

Primary records during the experiment were recorded on a Grass 8 channel electroencephalograph. Electrical gates for the determination of epochs in the behavioral test paradigm were also used to initiate the averaging epoch of 2.0 seconds in an average response computer (Mnemotron CAT). Initiation of the averaging analysis was arranged to precede presentation of the behavioral test situation by 300 msec on each trial. Completion of the approach occupied approximately 1.2 seconds. The output of the CAT computer was displayed on a chart recorder at the end of 20 and 40 approaches on each test day. Further analysis of these computed averages by auto- and cross-spectral computation required their transfer to an appropriate digital form for presentation to an IBM 7094 computer in the adjacent Health Sciences Computing Facility. This digitization could be performed in any of three ways; manually by visual examination of the record of the averaged output (Benson-Lehner OSCAR), by preparation of a punched card file from a numerical listing of the contents of each storage bin of the CAT computer at the completion of the averaging, or by preparation of a punched paper

tape of this output store in the CAT computer. The last technique required further processing of the paper tape to prepare a digital magnetic tape in IBM format. The techniques of cross-spectral analysis applied to these computed averages and the significance attaching to their interpretation have been described elsewhere (Adey, Walter and Hendrix 1961; Adey and Walter 1963; Walter 1963; Walter and Adey 1963).

RESULTS

A fixed dose level of LSD of 70 to 75 μg per kg was used in all experiments. Our previous studies had shown that this dosage in the cat could be anticipated to produce brief, high amplitude seizure-like bursts in hippocampal and subcortical leads in a quiet, dark environment for a period of 2 to 3 hours, but that these would be minimal or absent in the animal anticipating food reward in the test situation (Adey, Bell and Dennis 1962). Moreover, interference with task performance was minimal at this dosage.

The absence of clearly discernible effects on task performance in the period 1 to 3 hours after this dose of LSD was confirmed. Sample "resting" records taken immediately prior to testing in the T-maze were compared for days before and after LSD with those taken 1 to 2 hours after injection of LSD (Fig. 1). Careful visual inspection as well as auto- and cross-spectral analysis of the resting records have failed to reveal significant changes in hippocampal, subcortical or visual cortical leads which might be attributable to the drug. As will be described below, the computed averages from the right dorsal hippocampus during discriminative performance in the animal whose records appear in Fig. 1 were, however, considerably modified in the days following LSD. The gradual increase in the regularity of the computed average of these wave trains associated with attainment of higher

performance levels during training has been discussed in detail elsewhere (Adey and Walter 1963), and appears to relate to an increasing degree of phase-locking of these wave trains to the moment of presentation of the stimulus, rather than to such factors as an increase in amplitude of the waves in the individual bursts.

a. Effects in hippocampal records.

Typical records from the left dorsal hippocampus (LDH) and right dorsal hippocampus (RDH) in the course of the discriminative performance are shown in Fig. 2. In control records six days prior to receiving LSD (Fig. 2A), the right dorsal hippocampal record showed a typical regularization at about 5.5 c/sec in each of the 7 tests shown during approach to the food reward. By comparison, the records prior to commencement of the approach were essentially irregular, with slower dominant frequencies in the range 2 to 3 c/sec. These records from the right dorsal hippocampus are typical of those obtained from the dendritic layer of the pyramidal cells. Those from the left side (LDH) were from a less optimally placed recording dipole, and showed considerably less induced regularity during the period of discriminative approach. Similar records during the task performance two hours after LSD (Fig. 2B) and three days later (Fig. 2C) suggested a modest increase in regularity in the left dorsal hippocampal lead, but little else to distinguish these records from the controls.

The computed averages from the right dorsal hippocampus were markedly different in comparisons of pre- and post-drug trials (Fig. 3). These effects are visible in averages of both 20 and 40 trials. In control records (Fig. 3A), the regular average during the approach typically rose in a gradual fashion to a maximum over a period of 500 to 750 msec,

involving 2 or 3 waves of successively increasing amplitude. It declined thereafter in a relatively regular fashion. The envelope of the average exhibited a "spindle" shape. By contrast, similar averages on days after LSD (Fig. 3C) were characterized by a greater amplitude with the maximum occurring typically in the initial waves immediately following presentation of the situation, and with a slower and more regular decline than in control records. This modification persisted for 5 days after LSD, and was followed by reappearance of averages which resembled the controls (Fig. 3C, lowest trace).

As mentioned above, the left dorsal hippocampal lead exhibited relatively little theta rhythm in any control records by comparison with a comparable lead from the right hippocampus, due to minor discrepancies in its placement (histologically confirmed in zone CA1 of Lorente de Nó, where theta activity appears less well developed than in CA4). LSD appeared to induce increased rhythmic discharges in this lead on days after the drug, an inference from the raw records amply confirmed by the computed averages of wave trains during the discriminative performance (Fig. 4). Qualitatively, these modifications resembled those in the right hippocampus, with appearance of high amplitude phase-locked wave trains in the average, and with maximum amplitudes in the early waves of the train. This effect was maximal two to three days after LSD, and decayed to control levels after 5 to 7 days.

b. Late effects of LSD on computed averages from extrahippocampal structures.

Our previous studies have indicated that, as a concomitant to the highly rhythmic hippocampal wave trains in the course of the discriminative performance, there are similar trains of waves in other cortical and subcortical structures, including the midbrain reticular formation and

entorhinal (posterior pyriform) cortex. There is a strong similarity between the wave trains in the hippocampus itself and those in the entorhinal cortex, but from computed correlation analyses this identity of sustained rhythmic processes is much diminished in more remote structures, such as the subthalamus, midbrain reticular formation and primary sensory cortical area (Adey, Walter and Hendrix 1961). For these reasons, we have examined the effects of LSD on patterns of rhythmicity in averages from the pyriform cortex and reticular formation.

i) Posterior pyriform (entorhinal) cortex. By comparison with the effects in the hippocampus itself, computed averages of wave trains in the entorhinal cortex as a result of the third dose of LSD were less obviously modified (Fig. 5). There was an increase in the amplitude of the average in the early waves at the commencement of the discriminative performance, but little evidence of a sustained increase in regularity in the later parts of the approach epoch. It should be noted, nevertheless, that this increment in regularity was maximal 4 days after dosage with LSD (Fig. 5, 10/22/62) and declined toward control levels over the next 3 or 4 days.

ii) Midbrain reticular formation. Similar averages of activity in the midbrain reticular formation on the days before, during and following the first dose of LSD were also examined (Fig. 5). These records were from the same animal as those for the entorhinal cortex.

Here, the average of 20 runs made 110 minutes after LSD (Fig. 5B, 7/31/62) showed only rapid, irregular low amplitude components, although the primary EEG records at this time continued to exhibit large amplitude slow waves at the commencement of the approach performance (Fig. 6B), indicating that, as discussed elsewhere (Adey and Walter 1963), these slow

waves were insufficiently phase-locked to the moment of presentation of the test situation to appear in the computed average. This transient loss of a rhythmic average as an acute effect of the LSD contrasts sharply with the small but regular wave trains characterizing the first 700 msec of the average of the approach epoch immediately prior to dosage with LSD (Fig. 5B, 7/31/62). Each of the two averages on the LSD test day were for 20 test runs, so that direct comparison with the averages for 40 runs on the days before and after LSD requires caution. However, the high amplitude waves characterizing the early approach epoch on the pre- and post-LSD days (Fig. 5A and C) closely resemble the smaller waves of the control record on the LSD test day, so that the essentially irregular average immediately following the drug appeared to be a direct consequence of its early action.

Only minor differences were detected between the pre- and post-LSD averages in respect to the train of 3 waves characterizing the initial part of the approach epoch. A modest increase occurred in the amplitude of the first wave, and this was maximal 4 days after LSD (Fig. 5C, 8/4/62). There was also a distinct increment following LSD in the amplitude of the late wave component of the average which appeared about 1.2 seconds after initiation of the approach. This late component remained in excess of its amplitude in control averages for at least 12 days after LSD. Its onset was essentially coincident with attainment of the food reward. It was completely absent from the average immediately following LSD, and gradually reached a maximum 4 days later (Fig. 5C, 8/4/62).

In summary, the late effects of LSD were less obvious in the pyriform cortex and midbrain reticular formation than in the hippocampus itself. Those changes which could be detected followed a similar time course to

those in the hippocampus, maximizing about 4 days after drug dosage, and tending to disappear after 7 to 10 days.

DISCUSSION

This study has attempted to provide information on two important questions relating to the well known behavioral tolerance following a single dose of LSD and allied substances. Firstly, we have attempted to detect lasting changes in EEG patterns which might be induced by a single exposure to LSD, and to relate the persistence of the observed changes to the time course of the tolerance following such a single dose. Secondly, in view of the differential susceptibility of certain temporal lobe systems to LSD and related hallucinogenic agents (Adey, Bell and Dennis 1962; Monroe and Heath 1961), and their similar susceptibility to psychotomimetic agents of the cyclohexamine group (Adey and Dunlop 1960), we have examined aspects of the magnitude and persistence of these changes in the hippocampus itself by comparison with lasting changes in other regions, such as the rostral midbrain reticular formation, with which the hippocampal system is substantially interrelated (Adey, Segundo and Livingston 1957).

This study has clearly indicated that a single dose of LSD can induce changes in the computed average of hippocampal theta trains accompanying the discriminative performance, and that these changes reach a maximum about 4 days after the exposure. The increased regularity in the computed hippocampal average induced by LSD appears to decline more rapidly, however, than the tolerance to a second dose, which, from our previous observations, appears to last 2 to 3 weeks in the cat (Adey, Bell and Dennis 1962). It is entirely possible that more subtle electrophysiological

changes may persist beyond the 4 to 7 days noted here. The averaging technique used here can reveal with exquisite sensitivity the degree to which either theta wave trains or evoked transients accompanying the discriminative performance may show phase-locking to the presentation of successive behavioral tasks. This technique would not necessarily reveal subtle shifts in spectral content of these wave trains. Our attempts to disclose such small but even longer lasting effects with techniques of auto- and cross-spectral analysis are continuing but so far without success.

Evidence has also come from this study of a differential susceptibility of different brain regions to long-term effects of LSD. The sampling from different regions has necessarily been small, in view of the limited computing capability for simultaneous averaging from different brain regions, together with the need to compile sequential data from a single region over many days, and the necessarily long intervals between drug doses in a single animal. Nevertheless, the findings strongly suggest that the induced rhythmic modifications were best developed in the hippocampus itself and less obvious in the adjacent pyriform cortex. In the midbrain reticular formation, there was little effect on the rhythmic waves of the primary train immediately following task presentation. The regional susceptibility to late effects of LSD thus appears to substantially mirror the acute changes following LSD, in which spontaneous seizure-like discharges make their first appearance in the hippocampal system and propagate in a dose-dependent fashion to the nucleus ventralis anterior, subthalamus and rostral midbrain reticular formation (Adey, Bell and Dennis 1962; Monroe and Heath 1961). A basically similar pattern of propagation of subcortical afterdischarges following electrically induced

hippocampal seizures was described in the monkey by Poggio, Walker and Andy (1956).

The biochemical basis for these prolonged effects remains elusive. In recent years much attention has been directed to the biologically active amines as the substrate for many of the effects of both tranquillizing and hallucinogenic substances. Brodie, Pletscher and Shore (1955) proposed that brain tissue normally contains 5-hydroxytryptamine (serotonin) in bound form, and that it could function as a neurohumoral agent in brain tissue. Brodie and Costa (1962) have reviewed more recent evidence on the functional role of brain monoamines. Their studies suggest that reserpine releases serotonin from this bound store, and that it may be rapidly metabolized by the action of monoamine oxidase. It was found that whereas reserpine fell below detectable levels after 12 hours, its sedative effect persisted for more than 48 hours, and it was thus inferred that the sedative effect related to changes in brain serotonin concentration, rather than to the concentration of reserpine. Attempts to relate these changes to the effects of LSD remain doubtful, although Shore, Silver and Brodie (1955) have reported an interaction between serotonin and LSD in the central nervous system, with reduction of serotonin-induced sleep following hexobarbital anesthesia in the rat. The doses of LSD (10 mg/Kg) used by Shore et al. transcended by a substantial factor the doses used in the present study, which have been shown to be sufficient to induce prolonged tolerance in the cat (Adey, Bell and Dennis 1962).

Nevertheless, it appears that the mode of action of LSD in this respect may involve a trigger effect in the removal or modification of a substrate material. This view is supported by the findings of a cross-tolerance to

substances not closely related chemically, such as mescaline, LSD and BOL-148 (Balistrieri and Fontinari 1959). Tolerance has been considered as the basis of mechanisms of psychoses (Abramson, Jarvik, Gorin and Kirsh 1956; Cholden, Kurland and Savage 1955). A most striking prolongation of effects of single doses of LSD has been described in fish, with perseverant and unrewarding motor behavior following exposure to a solution containing 4 μg/ml of LSD. This behavior lasted for many weeks, and was prolonged by tryptamine but not antagonized by serotonin (Keller and Umbreit 1956). When given reserpine (20 μg/Kg for 3 days), the behavior returned to normal and remained normal.

It would thus appear that these manipulations with LSD and similar substances may modify metabolic substrates which, in turn, are essential to the normal patterns of EEG wave activity accompanying focused attention and discriminative performance. Although these effects can be sufficiently disruptive to destroy discriminative capability (Adey and Dunlop 1960; Adey, Bell and Dennis 1962), more subtle changes in EEG patterns can be detected by the techniques used here long after the acute phase of drug action. The question thus arises as to the relation between the EEG wave process and the coding, and perhaps storage, of information in cerebral systems (Adey and Walter 1963). Certainly, no unequivocal answer is possible at this stage, but a combined approach to the metabolic modifications induced by such agents as LSD and the electrophysiological concomitants of the behavioral changes which accompany them may offer keys not only to coding of information in the central nervous system, but to the mechanisms underlying its storage (Adey, Kado, Didio and Schindler 1963).

SUMMARY

The effects of LSD were studied in relation to changes induced in computed averages of epochs of EEG records during a discriminative task performance. Data are presented from two cats in a series of 18 animals repeatedly exposed to LSD over a period of many months. Computed averages were prepared from daily training tests of 20 and 40 trials. LSD (75 μg/Kg) was given in single doses by intraperitoneal injection at intervals of 3 to 6 weeks.

Computed averages of rhythmic hippocampal wave trains during approach performance showed an increase in amplitude and regularity following LSD, typically in the initial waves immediately following presentation of the situation. This modification was maximal 2 to 3 days after LSD, and decayed to control levels after 5 to 7 days. Similar analyses of records from the posterior pyriform (entorhinal) cortex indicated an increment in the early components of wave trains during discriminative performances, which also reached a maximum 2 to 3 days after LSD. Midbrain reticular activity showed only minor changes on days following LSD, also peaking about 4 days after drug dosage.

These findings indicate persistent electrophysiological effects of LSD beyond the period of acute drug action. However, these changes ran a shorter course than the tolerance to LSD exhibited by man and animals. They showed a differential distribution in different brain regions, with maximal changes in the hippocampus, and smaller effects in the entorhinal cortex and the rostral midbrain reticular formation. This differential susceptibility of hippocampal tissue is discussed in relation to a similar sensitivity to the acute effects of both LSD and psychotomimetic cyclohexamines, and to the pattern of propagation of hippocampal afterdischarges.

ACKNOWLEDGMENTS

This study was performed with the assistance of Grant B1883 from the National Institutes of Health, and Grant AF(AFOSR)246-63 from the U. S. Air Force. Computational analyses were supported by Grant NASA NsG 203-62 from the National Aeronautics and Space Administration.

Histological studies were performed by Miss Cora Rucker and Miss Arlene Koithan. Text figures were prepared by Miss Hiroka Kowta, and the computed analyses were materially assisted by Mrs. Martha Satin.

REFERENCES

Abramson, H. A., Jarvik, M. E., Gorin, M. H. and Hirsh, M. W. Lysergic acid diethylamide (LSD-25). XVII. Tolerance development and its relationship to a theory of psychosis. J. Psychol., 1956, 41: 81-105.

Adey, W. R., Bell, F. R. and Dennis, B. J. Effects of LSD-25, psilocybin and psilocin on temporal lobe EEG patterns and learned behavior in the cat. Neurology, 1962, 12: 591-602.

Adey, W. R. and Dunlop, C. W. The action of certain cyclohexamines on hippocampal system during approach performance in the cat. J. Pharmacol. exper. Therap., 1960, 130: 418-426.

Adey, W. R., Dunlop, C. W. and Hendrix, C. E. Hippocampal slow waves; distribution and phase relations in the course of approach learning. Arch. Neurol., 1960, 3: 74-90.

Adey, W. R., Kado, R. T., Didio J. and Schindler, W. J. Impedance changes in cerebral tissue accompanying a learned discriminative in the cat. Exper. Neurol., 1963, 7: 282-293.

Adey, W. R., Segundo, J. P. and Livingston, R. B. Corticifugal effects on brainstem conduction. J. Neurophysiol., 1957, 20: 1-16.

Adey, W. R. and Walter, D. O. Application of phase detection and averaging techniques in computer analysis of EEG records in the cat. Exper. Neurol., 1963, 7: 189-206.

Adey, W. R., Walter, D. O. and Hendrix, C. E. Computer techniques in correlation and spectral analyses of cerebral slow waves during discriminative behavior. Exper. Neurol., 1961, 3: 501-524.

Balistrieri, A. and Fontinari, D. Acquired and cross-tolerance to mescaline, LSD-25 and BOL-148. Arch. Gen. Psychiat., 1959, 1: 279-282.

Brodie, B. B. and Costa, E. Some current views on brain monoamines. Psychopharmacol. Service Bull., Washington, D.C., 1962, Vol. 5, part 2: 1-24.

Brodie, B. B., Pletscher, A. and Shore, P. A. Evidence that serotonin has a role in brain function. Science, 1955, 122: 968.

Cholden, L. S., Kurland, A. and Savage, C. Clinical reactions and tolerance to LSD in chronic schizophrenia. J. nerv. ment. Dis., 1955, 122: 211-221.

Jarvik, M. E. and Chorover, S. Impairment by lysergic acid diethylamide of accuracy in performance of a delayed alternation test in monkeys. Psychopharmacologia, 1960, 1: 221-230.

Keller, D. L. and Umbreit, W. W. Chemically altered "permanent" behavior patterns in fish and their cure by resapine. Science, 1956, 124: 407.

Lear, E., Suntay, R., Pallin, I. M. and Chiron, A. E. Cyclohexamine (C1-400): a new intravenous agent. Anesthesiology, 1959, 20: 330-335.

Monroe, R. R. and Heath, R. G. Effects of lysergic acid and various derivatives on depth and cortical electrograms. J. Neuropsychiat., 1961, 3: 75-82.

Poggio, G. F., Walker, A. F. and Andy, O. J. The propagation of cortical after-discharge through subcortical structures. A.M.A. Arch. Neurol. Psychiat., 1956, 75: 350-361.

Rothlin, E. Pharmacology of lysergic acid diethyl-amide (LSD) and some of its compounds. In S. Garattini and V. Ghetti (editors), Psychotropic Drugs. Elsevier, Amsterdam, 1957, 36-47.

Shore, P. A., Silver, S. L. and Brodie, B. B. Interaction of serotonin and lysergic acid diethylamide (LSD) in the central nervous system. Experientia, 1955, 11: 272-3.

Walter, D. O. and Adey, W. R. Spectral analysis of EEGs in the cat, recording during learning before and after subthalamic lesions. Exper. Neurol., 1963, 7: 481-501.

Walter, D. O. Spectral analysis for electroencephalograms: mathematical determination of neurophysiological relationships from records of limited duration. Exper. Neurol., 1963, 8: 155-181.

LEGENDS TO FIGURES

Fig. 1. Typical records in the "resting" state on days before LSD (A), on day of LSD dosage (B) and days after LSD (C). In each case, theta activity in hippocampal leads (LDH and RDH) and entorhinal cortex (L. ENT.) is well developed, and there are no gross effects attributable to the drug. Other abbreviations: R. SUBTHAL., right subthalamus; L.MB.RF., left midbrain reticular formation; R.VIS.CORT., right visual cortex.

Fig. 2. Typical records from left and right dorsal hippocampi (LDH and RDH) in same cat as in Fig. 1 during approach to food reward. Typical regularization of theta wave trains occurred during each discriminative performance.

Fig. 3. Computed averages of epochs of right hippocampal EEG records during approach performance on days before LSD (A), the day of LSD dosage (B), and days after LSD (C). The averages in the left column are for 20 runs, and on the right for 40. There was an increase in the amplitude and regularity of the averages following LSD. This maximized 3 days after the drug (C, 2/1/63), and declined thereafter.

Fig. 4. Computed averages of epochs of left hippocampal EEG, covering same test period as records from right hippocampus shown in Fig. 3. There was a marked increase in the amplitude and regularity of the averages after LSD, particularly on the third and fourth days (C, 2/1/63, 2/2/63).

Fig. 5. Computed averages of midbrain reticular (left column) and enthorhinal cortical activity (right column), preceding (A), during (B) and following (C) a single dose of LSD. Each average was for 40 approaches.

Fig. 6. Sample EEG records from entorhinal cortex (L. ENT.) and midbrain reticular formation (R.MB.RF.) during discriminative performance, showing control records one day before LSD (A), 90 minutes after LSD (B), and 4 days after LSD (C).